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ANTI-PROLIFERATIVE EFFECT OF POTENTIAL LSD1/COREST INHIBITORS BASED ON MOLECULAR DYNAMICS MODEL DERIVED FROM ITS INTERACTION WITH TETRAHYDROFOLATE COFACTOR

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Targeting cancer through epigenetics is a recent era, where a specific gene is manipulated without destroying it. Lysine-specific demethylase 1 (LSD1) is one of the enzymes that are associated with chromatin for post-translational modifications, where it demethylates lysine amino acid in the chromatin H3 tail. LSD1 is associated with its corepressor protein CoREST, and utilises tetrahydrofolate as a cofactor to accept CH2 from the demethylation process. Many studies showed that inhibiting LSD1 could potentially be used to treat cancer epigenetically. The fact that the cofactor is best bound to the active site inspired us to explore its interactions to LSD1/CoREST enzyme complex utilizing molecular dynamics simulation, which aids designing novel and potent inhibitors. Also, the conformational existence of the enzyme complex bound to the cofactor has been investigated. According to the molecular dynamics simulation study, LSD1/CoREST complex is present in open and closed conformations. Furthermore, tetrahydrofolate was found to bind to two binding sub-sites with different binding modes. The model derived from the molecular dynamics simulation study and the key contacts to the active site were used in the subsequent structure based drug design and *in silico* screening, which revealed a number of new chemical entities with a potential inhibitory effect of LSD1/CoREST complex. *In silico* mining on National Cancer Institute (NCI) database identified 60 promising and structurally diverse inhibitors. The cytotoxic activities of these compounds were tested against different cancer cell lines with different expression modes of LSD1/CoREST complex such as leukaemia K562, prostate cancer PC3 and neuroblastoma SH-SY5Y. All compounds were also tested against normal fibroblast cells to study their selectivity against cancer cells. Applying the abovementioned molecular modelling procedure yielded array of LSD1/CoREST inhibiters with IC50<5μM, when tested against different cancer cell lines. Three compounds inhibited the growth of PC3 prostate cells with IC50= (2.68, 2.08 and 2.95μM), four of them inhibited the growth of K562 leukaemia cells with IC50= (1.20, 1.92, 2.70 and 1.20μM) and three of them inhibited the growth of SH-SY5Y neuroblastoma cells with IC50= (0.27, 0.83 and 4.28μM). These compounds are excellent candidates for further optimization.

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MISSING CARCINOGENIC LINK BETWEEN BISPHENOL A (BPA) EXPOSURE AND BREAST CANCER

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Bisphenol A (BPA), used in the manufacture of clear plastic bottles and lining of food and beverage containers, has been implicated as a class 2B "Suspected" carcinogen and a teratogen by several countries. Within the cell, BPA interacts with MAPK and NFκB pathways that can lead to several tumorigenic events. Previous studies have either stopped at determining BPA induced DNA damage or cited the involvement of MAPK and NFκB pathways and only high dose BPA exposures have been reported that present non-conclusive tumorigenic evidence. These *in vitro* experiments demonstrate that low dose BPA not only causes single strand DNA breaks (SSBs) at 9nM but also causes more error prone double strand breaks (DSBs) at 17nM in the target cell lines. Author further used MCF-7 Human breast cancer and MCF-10A normal breast epithelial cell lines to compare tumorigenic events of BPA exposure. Being metabolized quickly by the liver to form DNA adducts, it can cause direct DNA damage and also act as an inhibitor of secretory pathway calcium ATPase1 (SPCA1). SPCA1 inhibition impacts the post-translational modification and intra-cellular transportation of insulin like growth factor 1 receptor (IGF1R) to the surface. Collectively these events raise the *in vitro* risk of a normal cell line MCF-10A to become tumorigenic.

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PARETO OPTIMAL BEAM PARAMETERS FOR 3D DYNAMICAL (B/GD) NEUTRON CANCER THERAPY

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Dynamical neutron cancer therapy (NCT) has recently been proved to be superior, in penetrating the surface of a (B/Gd)-loaded cancerous region, to a stationary neutron beam of the same intensity. By employing the relevant neutron diffusion theory, author demonstrate in this paper how the therapeutic utility index and the ballistic index for this kind of dynamical NCT form a nonlinear optimization process in which the neutron beam modulation frequencies and relative time delays form the control vector. A Pareto optimal control vector for this problem is identified and reported for the first time.

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A SURVIVIN REGULATED ONCOLYTIC ADENOVIRUS CAN IMPROVE THERAPEUTIC OUTCOME IN CHEMOTHERAPY RESISTANT LUNG CANCER

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The treatment of advanced lung cancer is restricted due to chemotherapy resistance even in the patients which initially show a good response. Author previously investigated a surviving promoter regulated conditionally replicating adenovirus (Sur-P-CRAd) for its anti-tumor potential along with cisplatin in three lung cancer cell lines; A549, H292 and H661 and found it very efficient. Also, surprisingly, CRAd in monotherapy proved very lethal against chemotherapy resistant sublines of above mentioned cells. They have suggested cisplatin-driven up regulation of CAR as a selective vulnerability of chemotherapy-resistant cancers. Keeping in mind the heterogeneity of lung cancer, this study employed two different lung cancer cells, H23 and H2126 and their resistant sublines H23/CPR, H2126/CPR, which were developed in our lab. RT-PCR and western blotting analysis confirmed that ABCB1 (MDR1) gene was overexpressed at both mRNA and protein levels in resistant sublines. Also, cocksackie-adenovirus receptor (CAR) expression found significantly up regulated in resistant cells as compared to chemo-sensitive cells. Resistant cells exhibited enhanced adenoviral transduction efficacy in X-gal staining assay which validated the up regulation of CAR. MTT assay, flow cytometry and scratch assays showed that cisplatin significantly decreases the viability of chemo-sensitive cells and its combination with CRAd synergistically inhibited cancer cell survival. Moreover, transwell assay revealed that CRAd pre-treatment restricts migratory ability of cancer cells. Epithelial to mesenchymal transition (EMT) markers investigation displayed that CRAd-treatment could reverse EMT event, but its molecular mechanism needs further elucidation. CRAd monotherapy experiments with resistant cells recapitulated similar results which established our hypothesis that CRAd alone is a very potent anticancer agent for resistant and metastatic tumors. These insights may prove to be a timely opportunity for the application of CRAd in recurrent drug-resistant cancers. Further studies are warranted to confirm the possible use of this innovative treatment approach in clinics and to move it from bench to bedside.